Phyto-Phospholipid Complexes: Innovative Approach to Enhance the Bioavailability and Therapeutic Efficacy of Herbal Extract

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Abstract

The herbal drug are used extensively for the treatment of the various diseases by the globe. The minimum side effects of medicinal plants attract people for its medicinal uses. The conventional dosage form of herbal medicine has certain limitation like low absorption, reduced bioavailability and lower penetration across biological membrane, it decrease their uses. Hence the introduction of novel drug delivery system namely Phyto-Phospholipid Complexes techniques resolve all these issues of herbal extract or plant actives. This advance technology technique reduced dose to produce desired therapeutic effect, improved stability due to chemical linkage, ability to permeate through skin systematic targeting to transit from hydrophilic to lipophilic environment and improved pharmacokinetic parameters. This review summarizes the latest investigations regarding the possible application of Phytosomes complexes for therapy of different diseases, their marketed formulation, mechanism of transportation through phytosome and future prospect. The prospectus of Phytosomes technique can suggest new directions and endless frontier as novel drug treatment.

1 Introduction

Presently demand of herbal medicines are enhanced in worldwide due to their safety, efficacy and folk acceptability. It has been realized that the herbal medicines have better compatibility with the human body since the chemical constituents present in them are a part of the physiological functions of living flora. The chemical constituents present in the medicinal plants imparts the therapeutic effect of the plant. In spite of the better therapeutic efficacy, the herbal medicine has certain limitation for the drug delivery, and higher doses required for the healing of diseases. The improvement in the field of herbal drug delivery was established with the objective to manage human disease more efficiently^{1,2}. Generally the plant actives demonstrated poor bioavailability due to their greater molecular size, and solubility property. Further, poor lipid solubility of bioactive component exhibit the partial capability to cross the biological membranes. The novel drug delivery system are design in such a way that it deliver the drugs with improved

bioavailability and release of drug in the controlled manner. The novel drug delivery system minimize the drug metabolism of active constituents and deliver the drug directly to targeted cells. This can improve the the bioavailability of extract by increasing their concentration at targeted cell and also minimizing the side effects arising due to the accumulation of drugs to the non-targeted areas^{3,4}.

The effective distribution of phytoconstituents can be accomplished by the help of novel drug delivery technology. The plant extract or phytoconstituents are incorporated in a suitable vesicle carrier for their efficient dissemination into the body. This mechanism aids in increasing solubility, stability, protection from toxicity, pharmacological activity and sustained delivery. The vesicular systems applied as a pharmaceutical carriers are such as liposomes, Phytosomes, nanostructure lipid carriers, solid lipid nanoparticles, niosomes, transfersomes, aquasomes, etc. The vesicular system consists of one or more concentric lipid bilayer, in which the amphiphilic blocks are confronted with water⁵⁻⁷. The

lipid based vesicular system improved retention and bio-distribution of drug due to their nano size. In addition the nano size carrier enhanced the drug pharmacokinetic, pharmacodynamic and in vitro stability due accumulation of drugs at preferably at the targeted site, this subsequently increases biodistribution and retention effect of drugs⁸⁻¹⁰.

Phyto-Phospholipid Complexes is referred as Phytosomes and is prepared by using the phospholipids and forming the complex between phytoconstituents or extract and phospholipids (Fig 1). It is advanced herbal drug delivery system, has outlined the vague bioavailability of lipid insoluble plant actives. Lipid insoluble herbal extracts can be redesigned into lipid compatible therapeutic candidate by chemically assimilating herbal extracts into phospholipids in specific ratio¹¹. Cellular vesicles produced

by phytosome methods avoid the destruction of water soluble active constituents by gastric secretion and microflora of gut. The active constituents complexes with phospholipid has different benefits like hepatoprotective action, reduced dose to produce desired therapeutic effect, improved stability due to chemical linkage, ability to permeate through skin systematic targeting to transit from hydrophilic to lipophilic environment has revolutionized the phytomedicine industry¹²⁻¹⁵. The Phyto-Phospholipid Complexes has resolved the limitation of therapeutic efficacy arising due to poor solubility and permeability of large size hydrophilic phytoconstituents across biological membranes. The present work highlights the importance and research prospects of Phyto-Phospholipid Complexes of plant actives.

Fig 1: Structure of Phyto-Phospholipid Complexes

2 Advantages of Phyto-Phospholipid Complexes

- Protecting drug from degradation
- Protection of drugs through biological interactions, and easily cross the membrane
- Increased the drugs pharmacokinetic and pharmacodynamic properties
- Increase the concentration of drug at the site of action
- Rate of drug release can be controlled
- Provide higher stability of extract
- Improved absorption of lipid insoluble extract orally as well as topically
- Improved drug entrapment efficiency
- As the absorption of active component is improved, its small dose can produce desired results.
- Formulation is easy as there is no problem in drug entrapment.
- Phytosomes are more useful than liposomes in skin care products.
- Phytosomes have significantly greater clinical benefit

3 Possible Mechanism of Phyto-Phospholipid Complexes

The reduced absorption of the extract or phytoconstituents is due to larger molecule size and poor miscibility with oils or other lipids. The larger size of active constituents are not absorbed from the intestine into the blood by simple diffusion. Further, the lipid

insoluble property of active constituents limits their capability to permit across the lipid-rich outer biological membranes of the small intestine incorporating enterocytes cell. The Phyto-Phospholipid Complexes developed to resolve these challenges and improved the bioavailability. The Phyto-Phospholipid Complexes are produced by reacting particular quantity of the phospholipid (phosphatidylcholine) with the extract or phytoconstituents (like simple flavonoids) in a non polar solvent. Phosphatidylcholine has bifunctional properties, the phosphatidyl moiety being lipophilic and the choline moiety being hydrophilic in nature. Precisely the choline head of the phosphatidylcholine molecule binds to these extract or phytoconstituents while the lipid soluble phosphatidyl portion comprising the body and tail which then surround the choline bound material. Consequently, the extract or phytoconstituents yield a lipid compatible molecular complex with phospholipids, also called as phyto-phospholipid complex. The chemical investigation demonstrate the unit phytosome is usually a plant active linked with at least one phosphatidylcholine molecule. The subsequent phyto-phospholipid complex is like a little microsphere or cell which easily cross the intestinal membrane and enhance the bioavailability of drug (Fig 2)¹⁶.

4 Reported improved bioavailability of Phyto-Phospholipid Complexes

The smaller size and lipophilic properties of Phytosomes are responsible to enhance the bioavailability of drugs. The numerous researchers scientifically documented the Phyto-Phospholipid Complexes better therapeutic and pharmacokinetic parameters compared to conventional dosage form. Some findings has been illustrated below:

Karole *et al.* (2019) reported Phytosomes of ethanol extract of *Bombax ceiba* produced better results of solubility study, entrapment efficiency, transition temperature, particle size and size distribution, optical microscopic study, zeta potential, transmission electron microscopy, stability studies and in vitro dissolution studies. The finding demonstrated synergistic antioxidant activity of phytosomes compared to individual extract¹⁷.

Fig 2: Possible Mechanism of Phyto-Phospholipid Complexes

Rathee *et al.* (2018) prepared Phytosomes of the fruits of *Citrulluscolocynthis* (L.), *Momordicabalsamina* and *Momordicadioica* extracts. Phytosomes were found to have antidiabetic activity comparable to metformin in low dose. HPTLC showed the presence of the phyto-constituent quercetin¹⁸.

Ittadwar *et al.* (2017) developed a novel formulation (Phytosome) of umbelliferone with phospholipid to improved permeability, solubility and hence better pharmacological action. The phytosomal complex was found to show better solubility in the water phase and oil phase, better permeation, better antioxidant activity and a better photo-protective activity when compared to umbelliferone¹⁹.

Vankudri *et al.* (2016) prepared Phytosomes of rutin by phospholipid complex and evaluated for antidiabetic activity. The findings demonstrated that the therapeutic efficacy of rutin Phytosomes enhanced compared to pure rutin²⁰.

Udapurkar *et al.* (2016) reported the applicability of Phyto-phospholipid complex vesicles for phytoconstituents and herbal extracts²¹.

Patil *et al.* (2016) documented the improved bioavailability of phytoconstituents incorporated into phospholipid complex²².

Sharma and Sahu (2016) formulated and characterized phytosomes containing ethanolic extract of *Abutilon indicum* and

Piper longum. The formulation exhibited better therapeutic effectiveness²³.

Saoji *et al.* (2016) formulated phospholipid-based complex of Standardized Centella Extract for the enhanced delivery of phytoconstituents. Thus, drug-phospholipid complexation appears to be a promising strategy to improve the aqueous solubility and bioavailability of bioactive phytoconstituents²⁴.

Vora *et al.* (2015) prepared and characterized standardized pomegranate extract-phospholipid complex as an effective drug delivery tool. Increased n-octanol solubility of the complex proved its increased lipophilicity. Dissolution studies revealed that the phospholipid covering may prevent the punicalagins to be released in gastro-intestinal tract, thus preventing their colonic microbial degradation²⁵.

Bhosale *et al.* (2015) documented the use and application of herbosomes as a novel drug delivery system for absorption enhancement²⁶.

Zahra *et al.* (2015) formulated Rutin-loaded Nanophytosomes, and findings indicate enhanced pharmacological activity²⁷.

Dhase *et al.* (2015) prepared and evaluated Phytosomes containing methanolic extract of leaves of *AegleMarmelos* (Bael). The pharmacological activity of Phytosomes was increased compared to crude extracts²⁸.

Zhang *et al.* (2014) prepared and evaluated the Solid dispersion of berberine phospholipid complex/TPGS1000/SiO₂. The therapeutic efficacy of formulations was found to be increased²⁹.

Abubakar *et al.* (2014) reported the effect of Phytochemical Constituents and Hypoglycemic Effect of Aqueous and Ethanollic Extracts of *MurrayaKoenigii* in Alloxan-Induced Diabetic Rats³⁰.

Gauttam and Kalia (2013) developed a phospholipids encapsulated polyherbal anti-diabetic formulation. In these study reported that the Phytoconstituents, despite having excellent bioactivity *in vitro* demonstrate less or no *in vivo* actions due to their poor lipid solubility, resulting in high therapeutic dose regimen; phospholipids encapsulation can overcome this problem³¹.

Khan *et al.* (2013) studied the advances and future prospects of phyto-phospholipid complexation technique for improving pharmacokinetic profile of plant actives³².

Raihan *et al.* (2012) evaluated the Antihyperglycemic Activity of Herbal Formulations on Alloxan Induced Rats. The herbal formulations exhibited significant antidiabetic activity³³.

Zaveri *et al.* (2011) prepared and evaluated drug phospholipids complex for increasing transdermal penetration of phyto constituents³⁴.

Kidd *et al.* (2009) described the bioavailability and pharmacological activity of Phytosome Complexes from Botanical Polyphenols namely Silymarin, Curcumin, Green Tea, and Grape seed extracts³⁵.

Bhattacharya (2009) worked on phytosome technology which enhances the bioavailability of herbal extracts. In Phytosomes technology the individual components of an herbal extract are bound to phosphatidylcholine. The emerging technology of drug delivery is being applied to phyto-pharmaceutical for the improvement of bioavailability of herbal extracts for medicinal applications³⁶.

Naik *et al.* (2008) performed study on Hepatoprotective effect of *Ginkgo select* Phytosome® in rifampicin induced liver injury rats and found significant Hepatoprotective activity in a dose dependent manner³⁷.

Sikarwar *et al.* (2007) evaluated Marsupsin–Phospholipid Complex to enhance its therapeutic activity. The outcomes demonstrated improved therapeutic activity³⁸.

5 Bioavailability Enhanced by Phyto-Phospholipid Complexes

Multiple studies have revealed that phyto-phospholipid complexes can boost the absorption of through oral topical route, hence it can increase the bioavailability and reduce the required dose. So, it can significantly improve therapeutic benefit (Table 1).

Table 1: Data of enhanced pharmacokinetic parameters by Phytosomes³⁹⁻⁴⁶

Parameter	T _{max} (h)	C _{max} (ng/ml)	AUC _(0–24 h) (ng/h/ml)
25-OCH ₃ -PPD	2.25	7.18	26.65
25-OCH ₃ -PPD-PC	2.10	28.07	97.24
Quercetin (10 ³)	0.50	0.67	2.04
Quercetin-PC (10 ³)	0.75	1.58	8.12
Quercetin	1.21	179.21	1368.26
Quercetin-PC	1.02	724.89	3321.05
Kaempferol	6.32	180.23	1139.59
Kaempferol-PC	5.83	323.56	2228.21
Isorhamnetin	7.21	195.96	1153.66
Isorhamnetin-PC	4.32	672.29	2722.37
Luteolin	2.5	3410.0	10,420
Luteolin–PC	2.0	9770.0	55,790
Berberine	0.5	66.01	384.45
Berberine-PC	2.0	219.67	1169.19
Oleanolic acid (OA) Solidified	0.313	59.5	259.6
OA-PC	0.46	78.7	360.6
Rosuvastatin	1.94	183.95	671.56
Rosuvastatin–PC	1.41	674.17	2018.59

20(R)-25-methoxyl-dammarane-3 β ,12 β ,20-triol - 25-OCH₃-PPD; Phospholipid complexes - PC

6 Marketed Phytosomes products

Today advanced technology bring revolution in the Pharma domain. The Pharmaceutical industries are manufacturing novel drug delivery system for better therapeutic efficacy. In this concern now plant active are formulated in the form of Phytosomes and many products are available in the market. Commercially available registered Phytosomes products by various manufactures as summarized in Table 2 claims safe and synergistic therapeutic benefits in various pathological conditions.

7 Future prospects

The preparation Phytosomes with the extract or plant active has appeared as leading technique for the improvement of Pharmacokinetic and therapeutic efficacy of extract which have poor bioavailability. The phyto-phospholipid complex has been widely developed by researchers as a novel drug carrier for systemic action. But still the Phytosomes have certain limitation

for its stability. Hence, it is prerequisite to explore research to resolve the issues of the preparation technique, stability and actual clinical superiority of these drug delivery systems. The use of hydrophilic solvents like ethanol in place of toxic organic solvent for the preparation of phyto-phospholipid complexes which increases their uses for clinical applications. The yield of the phyto-phospholipid complexes varied significantly in different studies from about 25% to more than 90% and has been attributed to different formulation factors like drug to phospholipid

ratio, temperature and duration of processing that have shown to affect the yield of carrier system. This aspect of the formulation has to be considered in future research works to get the formulation of best quality. Further statistical tools like factorial design, spherical symmetric designing and others can be used for optimizing the molar ratios of drug with phospholipids, along with the temperature and other variables to get maximum entrapment efficiency and a superior drug release profile.

Table 2: Commercial available Phytosomes of various therapeutic application¹⁶⁻²²

Biological Source	Commercial product	Therapeutic indications
<i>Aesculus hippocastanum</i>	Escin β sitosterol, Phytosome TM	Anti-oedema and vasoactive properties
<i>Ammi visnaga</i>	Visnadex TM	Improve microcirculation
<i>Centella asiatica</i>	Centella triterpenoid Phytosome TM	Skin disorders, antiulcer, wound healing, anti-hair loss agent
<i>Citrus aurantium</i>	Naringenin Phytosome TM	Antioxidant
<i>Crataegus oxyacanthoides</i>	Hawthorn Phytosome TM	Nutraceutical, cardioprotective and antihypertensive
<i>Cucurbita pepo</i>	Cucurbita Phytosome TM	Anti-inflammatory, Benign prostatic hyperplasia
<i>Fraxinus ornus</i>	Esculoside Phytosome TM	Vasoactive, anticellulite
	Ginkgoselect Phytosome TM	Cognition enhancer
<i>Gingko biloba</i>	Gingko bilobaterpene, Phytosome TM Gingko Bilobadimeric flavonoids Phytosome TM	Raynaud's disease, Antiageing, anti-asthmatic, Antiamnesic, antidepressant, Cardioprotective, dermatitis, Anti-Inflammatory
<i>Glycine max</i>	Soysselect Phytosome TM	Antiangiogenic, anticancer, cardioprotective, immunostimulatory and hypocholesterolemic
<i>Glycyrrhiza glabra</i>	Glycyrrhetic acid Phytosome TM	Anti-inflammatory, used in dermatitis
<i>Melilotus officinalis</i>	Lymphaselect TM	Anti-inflammatory, in oedema, thrombophlebitis
<i>Olea europaea</i>	Oleaselect Phytosome TM	Antioxidant, antihyperlipidemic, anticancer and anti-inflammatory.
<i>Panax ginseng</i>	Ginseng Phytosome TM	Nutraceutical, immunomodulatory
<i>Panicum miliaceum</i>	Millet Phytosome TM	Antistress, beauty food for skin, nails and hairs
<i>Curcuma longa</i>	Curcumin Phytosome TM , Curcuvet®(Meriva®)	Anti-inflammatory, osteoarthritis, anticancer
<i>Camellia sinensis</i>	Green tea Phytosome TM	Nutraceutical, anticancer, Antioxidant, atherosclerosis, hepatoprotective, antidiabetic, anti-inflammatory
<i>Echniacea angustifolia</i>	Echniacea Phytosome TM	Nutraceutical, immunomodulatory
<i>Pinus maritime</i>	Pycnogenol Phytosome TM	Anti-inflammatory, antiwrinkle, Antiallergic
<i>Radix puerariae</i>	Puerarin and phospholipid complex	Antiinflammatory, cardiovascular diseases

Biological Source	Commercial product	Therapeutic indications
<i>Ruscusa culeatus</i>	Ruscogenin Phytosome™	Anti-inflammatory, anti-ageing, Sunscreen agent
<i>Santalum album</i>	Ximilene and Ximenoil Phytosome™	Improve microcirculation
<i>Serenoa repens</i>	Phytosterols	Noncancerous prostate, Enlargement
<i>Silybium maranium</i>	Silybin Phytosome™ (Siliphos®)	Hepatoprotective, hepatitis, cirrhosis and inflammation
<i>Swertia alternifolia</i>	Swertia Phytosome™	Antidiabetic
<i>Syzygium cumini</i>	Madeglucyl Phytosome™	Antihyperglycemic, anti-inflammatory, antioxidant
<i>Terminalia serica</i>	Sericoside	Anti-aging, skin restructuring
<i>Vaccinium angustifolium</i>	VitaBlue Phytosome™	Anti-oxidant, improves vision, memory enhancer
<i>Vaccinum myrtillus</i>	Mirtoselect Phytosome™	Antioxidants, antiinflammatory, vasoprotective
<i>Vitis vinifera</i>	Biovin and leucoselect Masquiliers Phytosome™	Cardioprotective, systemic antioxidant, nutraceutical
<i>Zanthoxylum bungeanum</i>	Zanthalene Phytosome™	Soothing and Anti-reddening

There are numerous factors which govern the characteristic originality of Phytosomes in physical state such as physical size, membrane permeability, entrapment ratio, chemical constitution as well as the quantity and purity of the precursor starting chemical ingredients. The phyto-phospholipid complexes itself act as targeted carriers for tumor sites and reticuloendothelial system however this property can further be modified by controlling the particle size of the complexes.

8 Conclusion

Phyto-phospholipid complex technique has developed as progressive edge aspect in defining systemic absorption of extracts or plant actives. This technique has resolved the limitation of extract which decreased its bioavailability by reducing the size at nano level and making compatible with biological membrane of intestine. Further it enhance the lipid penetration at higher concentration with sustained and constant therapeutic levels in plasma, allows more quantity of plant active to reach at desired site of action. These novel drug delivery system can act as reliable candidates for improved drug dosage therapy.

9 Conflict of interest

None

10 Author's contributions

AS, AR and RM carried out literature review, while PKB, RY and SKG draft the manuscript. All authors read and approved the final manuscript.

11 References

- Shikha K. Babu, Smitha K. Nair, K. Krishnakumar. Phytosome and its therapeutic aspects. World J Pharm Sci 2019; 7(7): 12-19.
- More Minakshi S, Shende Mulchand A, Kolhe Deul B, J. N. M., Herbosomes: herbo-phospholipid complex an approach for absorption enhancement, Int. J. Biol. Pharm. Res., 2013; 4(9): 634–639.
- Gold J, Laxer D, Rochon P. Herbal remedies; a critical persepective. Ann R Coll Physician Surg Can. 2000; 33: 497-498.
- Tripathy S, Patel DK, Barob L, Naira SK. A review on phytosomes, their characterization, advancement & potential for transdermal application, Journal of Drug Delivery and Therapeutics. 2013; 3(3):147-152.
- Li J, Wang X, Zhang T, Wang C, Huang Z, Luo X, Deng Y. A review on phospholipids and their main applications in drug delivery systems, Asian J. Pharm. Sci. 2104; 10(2): 81–98.
- Theodosiou E, Purchartová K, Stamatis H, Kolisis F, Křen V. Bioavailability of silymarin flavonolignans: drug formulations and biotransformation. Phytochem Rev. 2014; 13: 1-18.
- Lu W, Lin C, King TD, Chen H, Reynolds RC, Li Y. Silibinin inhibits Wnt/β-catenin signaling by suppressing Wnt co-receptor LRP6 expression in

- human prostate and breast cancer cells. *Cell Signal*. 2012; 24: 2291-6.
8. Babazadeh A, Zeinali M, Hamishehkar H. Nano-Phytosome: A Developing Platform for Herbal Anti-Cancer Agents in Cancer Therapy. *Current Drug Targets*. 2018; 19: 170-180.
 9. Mazumder A, Dwivedi A, du Preez JL, du Plessis J. In vitro wound healing and cytotoxic effects of sinigrin-phytosome complex. *Int J Pharm* 2016; 498: 283-93.
 10. Verschoyle RD, Greaves P, Patel K, et al. Evaluation of the cancer chemopreventive efficacy of silibinin in genetic mouse models of prostate and intestinal carcinogenesis: relationship with silibinin levels. *Eur J Cancer*. 2008; 44: 898-906.
 11. Kumar S, Baldi A, Sharma DK. Phytosomes: A Modernistic Approach for Novel Herbal Drug Delivery - Enhancing Bioavailability and Revealing Endless Frontier of Phytopharmaceuticals. *J Develop Drugs*. 2009; 8(1): 1-8.
 12. Kumari P, Singh N, Cheriyan P, Neelam. Phytosomes: A novel approach for phytomedicine. *Int J Inst Pharm Life Sci*. 2011; 1: 89-100.
 13. Saha S, Sharma A, Saikia P, Chakrabarty T. Phytosomes: A brief overview. *Sch Acad J Pharm*. 2013; 2: 12-20.
 14. Amin T, Bhat S. A review on phytosomes technology as a novel approaches to improve the bioavailability of nutraceuticals. *Int J Adv Res and Tech*. 2012; 1: 1-15.
 15. Patel A, Tanwar Y, Rakesh S, Patel P. Phytosome: Phytolipid drug delivery system for improving bioavailability of herbal drugs. *J Pharm Sci and Bio Sci Res*. 2013; 3: 51-57.
 16. Agrawal VK, Gupta A, Chaturvedi S. Improvement In Bioavailability of Class-III Drug: Phytolipid Delivery System. *Int J Pharm Pharm Sci*. 2012; 4(1): 37-42.
 17. Karole S, Gautam GK, Gupta S. Preparation and evaluation of phytosomes containing ethanolic extract of leaves of *Bombax ceiba* for hepatoprotective activity. *The Pharma Innovation Journal* 2019; 8(2): 22-26.
 18. Rathee S, Kamboj A. Optimization and development of antidiabetic phytosomes by the Box-Behnken design. *J Liposome Res*. 2018; 28(2): 161-172.
 19. Ittadwar PA, Puranik PK. Novel Umbelliferone Phytosomes: development and optimization using experimental design approach and evaluation of photo-protective and antioxidant activity. *Int J Pharm PharmSci*. 2017; 9(1): 218-228.
 20. Vankudri R, Habbu P, Hiremath M, Patil BS, Savant C. Preparation and therapeutic evaluation of rutin-phospholipid complex for antidiabetic activity. *Journal of Applied Pharmaceutical Science*. 2016; 6(01): 090-101.
 21. Udupurkar P, Bhushure O, Kamble S, Biyani K. Phyto-phospholipid complex vesicles for phytoconstituents and herbal extracts: A promising drug delivery system. *International Journal of Herbal Medicine*. 2016; 4(5): 14-20.
 22. Patil PS, Salunkhe VR, Magdum CS, Mohite SK. Phytosomes: Increasing bioavailability of phytoconstituents. *International Journal of Universal Pharmacy and Bio Sciences*. 2016; 5(4): 81-94.
 23. Sharma S, Sahu AN. Development, characterization, and evaluation of hepatoprotective effect of *Abutilon indicum* and *Piper longum* phytosomes. *Pharmacogn Res*. 2016; 8: 29.
 24. Saoji SD, Raut NA, Dhore PW, Borkar CD, Popielarczyk M, Dave VS. Preparation and Evaluation of Phospholipid-Based Complex of Standardized Centella Extract (SCE) for the Enhanced Delivery of Phytoconstituents. *The AAPS*. 2016; 1: 102-113.
 25. Vora A, Londhe V, Pandita N. Herbosomes enhance the in vivo antioxidant activity and bioavailability of punicalagins from standardized pomegranate extract. *J Funct Foods*. 2015; 12: 540-8.
 26. Bhosale AP, Patil A, Swami M. Herbosomes as a novel drug delivery system for absorption enhancement. *World Journal of Pharmacy and Pharmaceutical Sciences*. 2015; 5: 345-355.
 27. Zahra H, Saeed G, Hamed H. Preparation and Characterization of Rutin-loaded Nanophytosomes. *Pharmaceutical Sciences*. 2015; 21: 145-151.
 28. Dhase AS, Saboo SS. Preparation and Evaluation of Phytosomes Containing Methanolic Extract of Leaves of *AegleMarmelos* (Bael). *International Journal of PharmTech Research*. 2015; 8(6): 231-240.
 29. Zhang Z, Chen Y, Deng J, Jia X, Zhou J, Lv H. Solid dispersion of berberine-phospholipid complex/TPGS 1000/SiO₂: preparation, characterization and in vivo studies. *Int J Pharm*. 2014; 465(1-2): 306-16.
 30. Abubakar NA, Oise AE, Saidu AN. Phytochemical Constituents and Hypoglycemic Effect of Aqueous and Ethanolic Extracts of *MurrayaKoenigii* in Alloxan-

- Induced Diabetic Rats. *IOSR Journal of Dental and Medical Sciences*. 2014; 13(9): 08-12.
31. Gauttam VK, Kalia AN. Development of polyherbal antidiabetic formulation encapsulated in the phospholipids vesicle system. *JAdv Pharm Technol Res*. 2013; 4(2): 108-17.
 32. Khan J, Alexander A, Saraf S, Saraf S. Recent advances and future prospects of phyto-phospholipid complexation technique for improving pharmacokinetic profile of plant actives. *Journal of Controlled Release*. 2013; 168: 50-60.
 33. Raihan O, Brishti A, Khalequeuzzaman M, Ahmed M. Antihyperglycemic Activity Evaluation of Antidiabetic Herbal Formulations on Alloxan Induced Rats Md. *Global Journal of Pharmacology*. 2012; 6(3): 226-230.
 34. Zaveri M, Gajjar H, Kanaki N, Patel S. Preparation and evaluation of drug phospholipids complex for increasing transdermal penetration of phytoconstituents. *Int. J. Inst. Pharm. Life Sci*. 2011; 1: 80–93.
 35. Kidd PM. Bioavailability and activity of phytosome complexes from botanical polyphenols: the silymarin, curcumin, green tea, and grape seed extracts. *Altern Med Rev*. 2009; 14: 226–246.
 36. Bhattacharya S. Phytosomes: Emerging Strategy in Delivery of Herbal Drugs and Nutraceuticals. *Pharma Times*. 2009; 41: 9-12.
 37. Naik SR, Panda VS. Hepatoprotective effect of Ginkgoselect Phytosome in rifampicin induced liver injury in rats: Evidence of antioxidant activity. *Fitoterapia*. 2008; 79(6): 439-445.
 38. Sikarwar MS, Sharma S, Jain AK, Parial SD. Preparation, Characterization and Evaluation of Marsupsin–Phospholipid Complex. *AAPS PharmSciTech*. 2008; 9(1): 129–137.
 39. Lu, M Qiu Q, Xiang L, Liu X, Sun J, Wang C, Lin X, Deng Y, Song Y. Phyto-phospholipid complexes (phytosomes): A novel strategy to improve the bioavailability of active constituents. *Asian Journal of Pharmaceutical Sciences*. 2019; 14: 265–274
 40. Chen ZP, Sun J, Chen HX, et al. Comparative pharmacokinetics and bioavailability studies of quercetin, kaempferol and isorhamnetin after oral administration of Ginkgo biloba extracts, Ginkgo biloba extract phospholipid complexes and Ginkgo biloba extract solid dispersions in rats. *Fitoterapia* .2010; 81(8): 1045–52.
 41. Zhang X, Zhang Y, Guo S, Bai F, Wu T, Zhao Y. Improved oral bioavailability of 20(R)-25-methoxydammarane-3 β , 12 β , 20-triol using nanoemulsion based on phospholipid complex: design, characterization, and in vivo pharmacokinetics in rats. *Drug Des Devel Ther*. 2016; 10: 3707–16.
 42. Zhang K, Zhang M, Liu Z, et al. Development of quercetin-phospholipid complex to improve the bioavailability and protection effects against carbon tetrachloride-induced hepatotoxicity in SD rats. *Fitoterapia* 2016; 113: 102–9.
 43. Khan J, Saraf S, Saraf S. Preparation and evaluation of luteolin–phospholipid complex as an effective drug delivery tool against GalN/LPS induced liver damage. *Pharm Dev Technol* 2016; 21(4): 475–86.
 44. Yu F, Li Y, Chen Q, et al. Monodisperse microparticles loaded with the self-assembled berberine-phospholipid complex-based phytosomes for improving oral bioavailability and enhancing hypoglycemic efficiency. *Eur J Pharm Biopharm*. 2016; 103: 136–48.
 45. Jiang Q, Yang X, Du P, Zhang H, Zhang T. Dual strategies to improve oral bioavailability of oleanolic acid: enhancing water-solubility, permeability and inhibiting cytochrome P450 isozymes. *Eur J Pharm Biopharm*. 2016; 99: 65–72.
 46. Beg S, Raza K, Kumar R, Chadha R, Katore O, Singh B. Improved intestinal lymphatic drug targeting via phospholipid complex-loaded nanolipospheres of rosuvastatin calcium. *RSC Adv*. 2016; 6(10): 8173–87.
 47. Singh A, Saharan VA, Singh M, Bhandari A. Phytosomes: Drug delivery system for polyphenolics phytoconstituents. *Iranian J of Pharma Sci*. 2011; 7(4): 209-19.
 48. Pierro FD, Menghi A, Barreca A, Lucarelli M, Calandrelli A. Greenselect® phytosome as an adjunct to a low-calorie diet for treatment of obesity: A clinical trial. *Alt Med Rev*. 2009; 14: 154-60.
 49. Gandhi A, Dutta A, Pal A. Recent trends of phytosomes for delivering herbal extract with improved bioavailability. *J Pharmacog and Phytochem*. 2012; 1(4): 6-14.
 50. Pandey S. Phytosomes: Technical revolution in phytomedicine. *Inter J Pharm Tech Res*. 2010; 2: 627-31.
 51. Das MK, Kalita B. Design and evaluation of phytophospholipid complexes (Phytosomes) of rutin for transdermal application. *J Appl Pharma Sci*. 2014; 4(10): 051-57.

52. Maiti K, Mukherjee K, Gantait A, Saha BP, Mukherjee PK. Enhanced therapeutic potential of naringenin phospholipid complex in rats. J Pharm Pharmacol. 2006; 58: 1227-33.
53. Naik S, Pilgaonkar V, Panda V. Evaluation of antioxidant activity of *Ginkgo biloba* phytosomes in rat brain. Phytother Res. 2006; 20: 1013-6.